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Ocular drug delivery system: Approaches to improve ocular bioavailability

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Abstract

The aim of this review is to present an update on the current knowledge within this field of ocular drug delivery. There is a lots of route of drug delivery, but today one of them, the ocular drug delivery system becomes the most compulsive and attractive attempt in front of pharmaceutical scientists. Ocular drug delivery has always been a formidable task in the area of pharmaceutical research due to distinctive structure and function of the eye. Different attempt in ocular drug delivery have been made to enhance the bioavailability and to increase the contact time of topically applied drugs to the eye. In an ophthalmic dosage form the less bioavailability is due to the tear production, achieving less absorption, short term residence time, and less permeability of corneal epithelium. Immediate pre-corneal elimination is a biggest problem in ocular drug delivery. In order to solve this problem, researchers developed a new system; in-situ gel forming system. This formulation undergoes phase transition in the eye to form gel, thus prolonging the precorneal contact time which will result in enhance ocular bioavailability for prolonged therapeutic action ointment, suspensions and gelled systems are also used.

Keywords: Ocular drug delivery, precorneal, bioavailability.

Introduction

Ocular drug delivery is most compulsive and demanding delivery system in front of the pharmaceutical scientist. The unique structure, function, and biochemistry of the eye provide this organ highly impermeable to foreign substances. An important searching to the formulator is to overcome the protective barriers of the eye without causing long term tissue damage[1]. These types of barriers are highly affecting the bioavailability of ophthalmic drugs. In ophthalmic drug delivery system, the rapid and extensive elimination is the main problem of conventional eye drop from eye.

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This difficulty results in huge loss of drug. Only a less amount of drug penetrates the corneal layer and passes to inner tissue of eye. The main division of drug loss contain lachrymal drainage and drug dilution by tears. This satisfaction reduces the ocular bioavailability and conduct to undesirable side effect and toxicity[2].
To optimize ophthalmic drug delivery systems the following characteristics are required:

- Sterility
- Isotonicity
- A good corneal penetration
- Minimum protein binding
- Less drainage tendency
- Buffer/ pH adjustment
- A continued contact time of drug with corneal tissue
- Easiness in installation and removal.
- A non-irritative form
- Good rheological properties[3-5]

Physiology of sight

Light waves travel at a speed of 300 000 kilometres (186 000miles) per second. Light is reflected into the eyes by objects within the field of vision. White light is a combination of all the colours of the visual spectrum (rainbow), i.e. red, orange, yellow, green, blue, indigo and violet. This is demonstrated by passing white light through a glass prism which bends the rays of the different colours to a greater or lesser extent, depending on their wavelength[6]. In the field of visual spectrum red colour light has the longest wavelength and violet colour has the shortest wavelength.This range of colour is the spectrum of visible light. In a rainbow, white light from the sun is broken up by rain drops, which act as prisms and reflectors[7].The main function of the eye is to receive the light which is converted into visual image on the retina from where it is translated into a correct picture by the involvement of visual centres in the brain. In each hemisphere of the brain of optic nerve fibres from the eyes reach the optic lobe which contains the visual centres. Impulses to neurons in these lobes register the image. When light falls on the rhodopsin containing cells of retina, the rhodopsin molecules split into separate retinene and opsin component and a nerve impulse is produced at the same time. In the darkness of the eyeball and with the help of respiratory energy, retinene and opsin recombine again. This recombination generates the image. In very intense light and in the absence of vitamin A, this reaction does not take place, therefore image formation becomes impossible. In a way image formation is a chemical reaction which needs moderate light to act as a catalyst. An object to be pictured on the retina forms a series of points corresponding to rods and cones and the image is the sum total of all these points. Although there forms an inverted image like that in a camera, yet the visual centres of the brain do the job of giving a correct orientation to the inverted image under the combined effort of muscles, and gravitational pull[8]

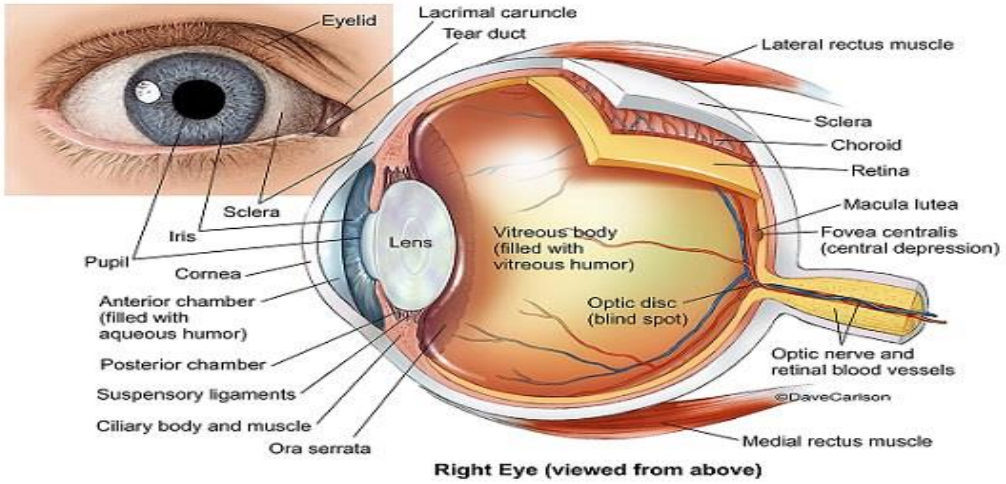

Fig 1: Structure of Eye[3]

Disease of eye

Myopia (Near Sightness)

In this disorder, a person can only see near objects and has difficulty in having a correct sharp focus of the distant objects because the eyeball is oblong or elongated so that the distance between the lens and the retina is more than required. The image falls short of reaching the retina and a person experiences a blurred image. Spectacles with concave lenses are needed to extend the focus to the retina

Hypermetropia (Far Sightedness)

This defect is reverse of myopia as the eyeball is shorter than its normal size, whereby the focus of image extends beyond retina because it is nearer to the lens instead of being at its original position in the normal eye. A person with this defect has difficulty in

seeing the near objects but can clearly see the distant objects. Spectacles with convex lenses are needed to restore normal vision.

Astigmatism

This disorder does not permit a person to see clearly the objects irrespective of their distance from the eye due to the uneven curvature of the lens. Accordingly, uneven convex lenses are needed to bring the focus to the right place on the retina. Such lenses are made by girding them as per requirements.

Presbyopia

Presbyopia is generally a disorder of old age when the lens are starts losing its elasticity so that it fails to from the images to near objects while distant vision is normal. A person suffering from this defect has to keep the object or a paper as far away from him as required improving visibility. Convex lenses are needed for correcting the disorder.

Cataract

Cataract is also an abnormality of the lens in which it becomes partially or completely opaque so that no light gets into the eye. The commonest reason is ageing while injury, heredity and diabetes, etc. are other possible reasons. It is the commonest disorder known as sfaid motia which can be cured by removing the defective lens[9]

Glaucoma

Glaucoma is another common cause of blindness. In this disorder of the eye, there is failure of the drainage of liquid from the anterior chamber as a result of which, more than the required amount accumulates in it which cause pressure on the optic nerve and retina. Increased pressure hinders the normal supply of blood and nutrients. However, the disease is curable when detected and attended early. It is also known as kala motia which is common in older persons[10].

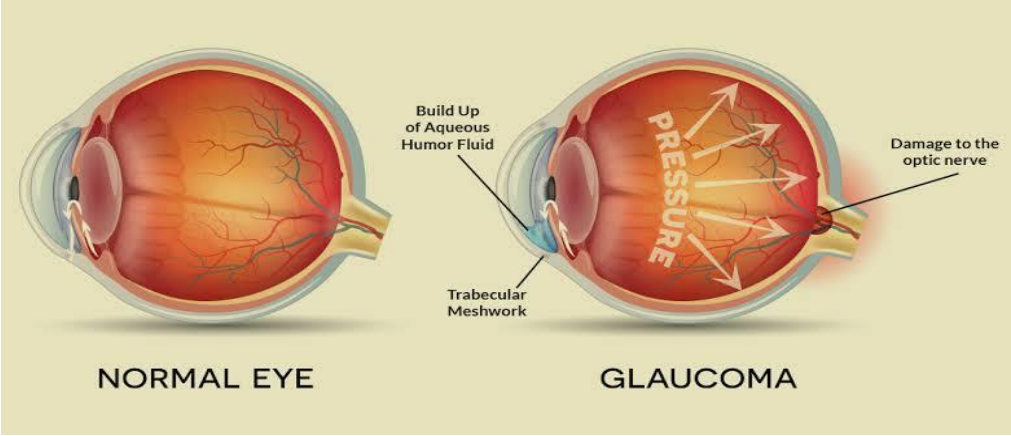

Fig 2:Normal eye and Glucoma

Keratitis

Keratitis is the inflammation of cornea which may also get damaged by injury or serious infection. Corneal grafting or replacement with a normal cornea from the donor is a part of the publicity that is given to the phenomenon of the donation of eyes after death.

Conjuctivitis

One often hears of epidemic of this disease in which eyes become red and there is continuous watery discharge from them. It is caused by infection of the conjunctiva which is curable by easily available formulations. Photophobia or intolerance to light is associated with this disorder.

Trachoma

It is also a common disorder of the eyes due to viral infections of the conjuctiva that can assume epidemic proportions when allowed to spread due to carelessness in treatment[11].

Dry Eye

Dry eye is a condition in which a person doesn't have enough quality tears to lubricate and nourish the eye. If the composition of tears is changed, or an inadequate volume of tears is produced, the symptom of dry eye will result. Dry eye conditions are not just a cause for ocular discomfort where it also results in corneal damage[12].

Ocular Drug Delivery System

Ophthalmic dosage formulations are classified as conventional and non – conventional (newer) drug delivery system. Various formulation like In situ gelling, use of mucoadhesive polymers, polymer coated nano-particles and microspheres, micro emulsion and liposomal formulation are used[6]. There are most frequently available ophthalmic preparation such as drops and ointments about 70 % of the eyes dosage formulations in the market. These formulations delay the elimination of active ingredient from eye, also improve bioavailability of the drug and increase corneal penetration of drug molecule[13].The primary approaches in the design of control release ocular drug delivery system attempt to slow down the drainage of drug by tear flow. The conventional and novel drug delivery system are explained as below[11]

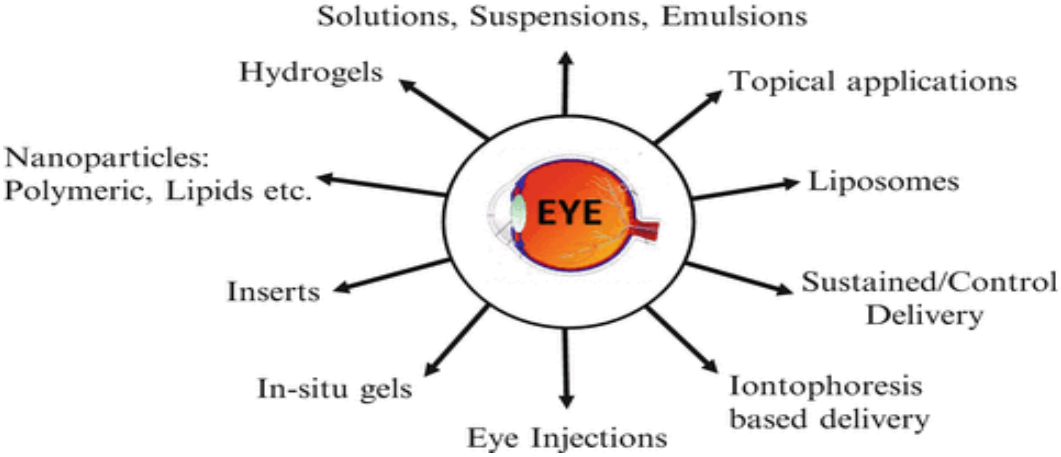

Fig 3:Different formulations for eye

Conventional Ophthalmic Systems

Most of the topically administered dose is lost due to reflux blinking and only 20% of instilled dose is retained in the precorneal pocket, conventional ocular drug delivery system have some limitations along with them like poor bioavailability, less resistance time of drug in pre corneal area[11]. Some of the important types of conventional ophthalmic preparations are:

Solutions

Drugs which are active at eye or eye surface are widely administered in the form of Solutions. Ophthalmic solutions are sterile solution and they are free from foreign particle[14]. Solutions are widely used dosage forms for topical delivery of therapeutics to the eye[15]. In an ocular drug delivery system the major factor that affect the formulations are solubility, ocular toxicity, pka, ph effect, tonicity, buffer capacity, viscosity, compatibility with other ingredients in the formulation, preservatives to be used, comfort when instilled into the eye[5].

Advantages

1 Simplicity of large scale manufacture
2 convenience and
3 Usually do not interfere with vision of patient

Disadvantages

1 Solution having very short time interval so its rapid precorneal elimination from the eye.
2 The retention of a solution in the eye is influenced by viscosity, hydrogen ion concentration and the instilled volume.
3 75% is lost via nasolacrimal drainage so having poor bioavailability.
4 Occular drug delivery having non sustained action.
5 To be administered at frequent intervals.

Suspensions

Suspension may be defined as dispersion of finely divided insoluble API in an aqueous solvent consisting of a suitable suspending and dispersing agent. An ocular topical drop these are another class of non – invasive drug carrier system. Ophthalmic suspension

improves the bioavailability because it retains in precorneal pocket and thereby improve drug contact time and duration of action relative to drug solution[13]. These are more complex when compare the eye drop[15].

An ophthalmic suspension contains many excipients like suspending agents, wetting agents, buffers and preservatives. Suspending agents are used to avoid the sedimentation and improve rheological property of a suspension. Generally ophthalmic suspension used suspending agents are includes cellulosic derivatives such as methyl cellulose, caboxy methyl cellulose, and hydroxyl propyl methyl cellulose, synthetic polymers such as carbomers, poloxamers, and polyvinyl alcohol. Wetting agents are used to decreases the contact angle between the solid surface and the wetting liquid. Generally used wetting and solubilizing agents are Benzalkonium chloride, Benzethonium chloride, Cetylpyridinium chloride, Nonoxynol 10, Octoxynol 9, Poloxamer, Polyoxyl 50 stearate, Polyoxyl 20 cetostearyl ether, Polyoxyl 40 stearate[14].

Emulsion

Ophthalmic emulsions are generally dispersions of oily droplets in an aqueous phase, there should be no evidence of breaking or coalescence[16]. An emulsion based formulation has an advantage to improve solubility and bioavailability of drugs. Two types of emulsion are there which are commercially used as vehicles for active pharmaceuticals: oil in water (o/w) and water in oil (w/o) emulsion systems. Because of less irritation and better ocular tolerance o/w emulsion is common and widely preferred over w/o system for ophthalmic drug delivery[13]. The advantage of this type of formulations is prolonging release of drug from vehicle. Patient non compliance is the demerits of emulsion[17].

Eye drops: Eye drops are saline-containing drops used as an ocular route to administer[17].Eye drops are used only for anterior segment disorders of eyes because insufficient drug concentrations reached in the posterior tissues using ocular drug delivery system. Hydrogen ion concentration, osmolality, viscosity and instilled volume are some property that effect retention of a solution in the eye. Only less than 5% of the drug is absorbed after administration of the drug into eye, major fraction of the administered drug get washed away with the lachrymal fluid or absorbed systemically in the nasolacrimal duct and pharyngeal sites[6]. The important constituents present in these may be antihistamines, steroids which are commonly used in glaucoma patients, beta receptor blockers, prostaglandins, topical anaesthetics and many others. Some eye drops marketed do not contain any active pharmaceutical agent and they are used only for a lubricating and tear replacement purpose[18].

Recent work done in eye drops New Eye Drops Can Dissolve Cataracts with No Need for Surgery Zhang and his research team went on to develop eye drops that contained lanosterol as a drug treatment for cataracts[17].

Ointment

Ophthalmic ointments are the semi solid dosage form and usually prepared by using mixtures of semisolid and solid hydrocarbons like paraffin which have a melting point or softening point is nearby to body temperature and are non irritating to the eye[5]. Using ophthalmic ointment vehicle enhance contact time with the external ocular surface can be achieved but, some demerits like, blurring of vision can limits its use. Pilopine HS gel containing pilocarpine was used to provide sustain action over a period of 24 hours. A number of workers reported that ointments vehicles can improve the corneal contact time of many drugs administered by topical ocular route, thus prolonging duration of action and enhancing ocular bioavailability of drugs[19]. Ophthalmic ointments are applied externally on the surface of eye. This dosage form less preferred as compared to the emerging dosage ophthalmic forms because occurrence of some patients irritation and blurred vision[18].

Sprays

Eye spray is mainly used for pupil dilation or for cycloplegics (paralysis of the cilliary muscle of the eye) examination. Even ophthalmic sprays are not commonly used, but some patients with mydriatics or cycloplegics use alone or in combination in the form of eye spray[20]

Viscous Solution

These types of solutions are prepare in laboratory scale by adding some polymer and enhancing the viscosity of the eye preparations ,so that in the precorneal area the residence time could be increased hence a greater transcorneal penetration of the drug into the anterior chamber. In terms of improvement in bioavailability it has minimal effects in humans. The viscous solution is prepared by adding some viscosifying agents like cellulose, polyacrylic acid. Carbomer, Xanthan gum also holds an important place in increasing viscosity of these agents[18]. Some other polymers used are methylcellulose, polyvinyl alcohol (PVA), polyvinylpyrrolidone (PVP), hydroxyethylcellulose, hydroxypropyl methylcellulose (HPMC), and

hydroxyl-propylcellulose. Natural polymers such as HA, veegum, alginates, xanthan gum, gelatin, acacia., and tragacanth can also be used as viscosity enhancers. However, these suffer the drawback of harboring bacteria and fungi[5].

Gels

Ophthalmic gels are composed of mucoadhesive polymers that provide localized delivery of an active ingredient to the eye. These polymers extend the contact time of the drug with the biological tissues and improve ocular bioavailability. Most commonly used polymers in ocular gels are gellan gum, alginic acid, xyloglucan, pectin, chitosan, poloxamer, gellan gum, sodium alginate[16].

Advantages

1. Increase contact time.
2. Greater storage stability.

Disadvantages

1. Blurred vision but less then ointment.
2. Poor patient compliance.

Recent work done: A new eye gel containing sodium hyaluronate and xanthan gum for the management of posttraumatic corneal abrasions.

Francesco Faraldi *et al* investigates the effects of an ophthalmic gel containing sodium hyaluronate and xanthan gum in addition to the antibiotic netilmicin in the management of traumatic corneal abrasions[17].Gel formation is an extreme case of viscosity enhancement through the use of viscosity enhancers. Instead of giving multiple doses in case of solutions the dosing interval can be reduced in case of gels Cellulose acetate phthalate dispersion constituted a microreservoir system of high viscosity. Poloxamer 407 is used as an ophthalmic vehicle for pilocarpine delivery and found that the gel formation enhances the activity of pilocarpine. Timolol maleate form thermo gelling drug delivery system composed of cellulose ether ethylhydroxylethylcellulose.The effect of Flurbiprofen, which is a NSAID, formulated in Pluronic F-127 and carbopol 940. Gelrite is a polysaccharide which is also known as gellan gum. It forms a clear gel in the presence of mono or divalent cations. The high viscosity of the gel, however, results in blurred vision and malted eyelids which substantially decreases patient acceptability. Sterilization is another drawback for large scale production[2]. A number of workers reported that gels vehicles can prolong the corneal contact time of many drugs administered by topical ocular route, thus prolonging duration of action and enhancing ocular bioavailability of drugs[19]

Noval approaches towards ophthalmic drug delivery

In situ forming gels

Ophthalmic in situ gel system was developed in 1980s, this type of drug delivery is most widely used it is reducing the drainage of the drug from cornea due to increase viscosity hence bioavailability automatically enhanced. In-situ gelling system can be effect by temperature, pH or ion activation[16] These preparation gave the better release property of a drug over a long period of time in the rabbit's eye as compared to conventional eye drops[20]. Ophthalmic in situ system basically found in liquid form but they undergo sol to gel phase transition as they are administer into the eye due to a particular stimulus. After becoming a gel, these remain for a much higher extent in the eye as compared to the conventional dosage forms[21].

Method of preparation of in-situ ocular gel

Methods

Cold Method

HEC was dissolved in water was added to Pluronic solution (prepared by dispersing Pluronics over the distilled water with continuous stirring (500rpm) and it is kept in refrigerator (4 degree) until the Pluronics dissolves (Magnetic stirrer) (24Hour)

⇩

Mixed both solution @300 rpm on magnetic stirrer, 500mg drug solution was prepared by dissolving in water was prepared and added to above solution.

⇩

0.02% Benzalkonium chloride solution was added to above solution as preservative and the pH was adjusted to 7.4 using 0.5M NaOH, which is then sterilized in Autoclave @ 121 degrees for 20 minute[9]

This is a system were the formulation behave like solution form, which changes the behavior to gel when it is instilled into the eye.

Occular Insert

This novel ophthalmic drug delivery as they show a much higher extent of controlled, sustained drug release as compared to the conventional forms[18]. Ocular insert are solid and semi solid dosage form placed into the conjunctival sac. Ocular inserts are aseptic, thin, multilayered, drug loaded an efficient drug concentration within the intended tissues[22] -

Dexamethasone, Pilocarpine nitrate, Tropicamide and Timolol Maleate are some example of ocular insert[23]

Microemulsion

Micro emulsions are stable dispersions of water and oil by using a surfactant and co-surfactant in a manner to reduce interfacial tension. Selection of aqueous phase, organic phase and surfactant/co-surfactant systems are critical parameters which can affect stability of the system[17]. These types of ocular drug delivery have an advantage of very high thermodynamic stability, increase solubility, and improved corneal permeation; hence improve the ocular bioavailability of the drug[5] .Micro emulsions have a transparent appearance, with thermodynamic steadiness and a small droplet size in the dispersed phase (aqueous and non aqueous phase) (<1.0µm). Due to their intrinsic properties and specific structure micro emulsions are an interesting substitute to ophthalmic formulation[14]. Micro emulsion showed the greatest miotic response and duration of action, indicating high ocular bioavailability. Various micro emulsion formulations for ophthalmic use such as timolol, sirolimus, and chloramphenicol were formulated with improved stability, solubility, and bioavailability.

Nanosuspension

Nano suspensions have proceeded as a favourable procedure for the efficient delivery of hydrophobic drugs delivery they are not only enhanced the rate and extent of ophthalmic drug absorption but also the intensity of drug action with significant extended duration of drug effect[24].Nano suspensions are poorly water-soluble drug suspended in an appropriate dispersion medium stabilized by surfactants. Nanosuspension has an advantage to improved solubility of the drug, enhanced bioavailability, and reduced irritation to the eye. Results indicated that the nano suspension has shown greater anti-inflammatory activity when compared with microsuspensions[5].The two technique, media milling and high pressure homogenization are have been used commercial preparation of nanosuspension[17].

LIPOSOMES: Liposome's are multilamellar or unilamellar lipid vesicles made up of natural lipids and about 25 –10 000 nm in diameter. Liposomes can be formulated by sonication of dispersion of phospholipids, reverse phase evaporation, solvent injection and detergent removal or calcium induced fusion method. These formulations are mainly composed of phosphatidylcholine and other constituents such as cholesterol and lipid-conjugated hydrophilic polymers[25].

Phospholipids used Phosphotidylcholine, Phosphotidic acid, Sphingomyline, Phosphotidyl-eserine, Cardiolipine. Liposomes are Non-toxic, Biodegradable and biocompatible in nature. Liposomes can bind closely on the eye surface to increase the residence time and thus enhance drug absorption and bioavailability[22]

Niosomes

Ocular niosomes are nonionic surfactant vesicles that used in the delivery of hydrophobic or amphiphilic drugs.Niosomes is developed to avoid the limitations od liposomes as they are chemically entrap both hydrophobic and hydrophilic drugs[26]. They do not require special handling techniques for preparation and they are non toxic. Niosomes are non-ionic surfactant based multilamellar (>0.05µm), small unilamellar (0.025-0.05µm) or large unilamellar vesicles (>0.1µm) in which an aqueous solution of solute(s) is entirely enclosed by a membrane resulted from organization of surfactant macromolecules as bilayers. The advantage of niosomes are Better patient compatibility and better therapeutic effect than conventional[17].The characterization of niosomes are ,biodegradability, biocompatibility, nonimmuno -genicity and absence of various drawbacks related with liposomes, such as high cost and the fluctuating purity troubles of phospholipids[22]

Nanoparticle

Nanoparticles are solid, submicron, colloidal particles made up of biodegradable polymer that combines the capabilities of stimulus response and molecular recognition hold a pronounced aptitude in ocular drug delivery and the ranging in dimension from 10 to 1000 nm. In ocular nanoparticle the drug molecules are present in dissolved, entrapped, adsorbed or covalently attached form[22]. Bioavailability can be enhance by using carriers, in this system the drug gets bind to these carrier molecules and they provide a much higher absorption and penetration rate in the eye[18].Ophthalmic nanoparticle have been mainly produced by emulsion polymerization method for drug liberation. In this process a scantily soluble monomer is dissolved in the continuous phase which can be aqueous or organic. Polymerization is started by chemical instigation or by irradiation with gamma rays, ultra violet or visible light. The resources that have been mainly used fur ophthalmic nanoparticles are polyalkyl cyanoacrylates. Nanoparticles are prepared

by using bioadhesive polymers to provide sustained effect to the entrapped drugs[27].Polymers are used in nanoparticles are (PLAs), polycyanoacrylate, poly (d,l-lactides), natural polymers can be used effectively for efficient drug delivery to the ocular tissues[14]

Dendrimers

Dendrimers, a nanoparticle based drug delivery system, hold a lot of implementations in pharmaceuticals such as improving the solubility of miserably soluble drugs, improving the delivery of DNA and oligonucleotides, targeting drug at specific receptor site, and possess the ability to mimic as carrier for the evolvement of drug-delivery systems The utilitization of aqueous PAMAM dendrimers has been revealed to be of importance in the ocular route. In fact, PAMAM dendrimers displayed physicochemical attributes (pH, osmolality, viscosity) that are congruous with ocular formulations[22].Dendrimers can successfully used for different routes of drug administration and have better water-solubility, bioavailability and biocompatibility[17]. Dendrimers provide solutions to some complex delivery problems for ocular drug delivery. Some recent research is dendrimers for ocular drug delivery include PAMAM dendrimers that were studied by Vandamme and Brobeck as ophthalmic vehicles for controlled delivery of pilocarpine and tropicamide to the eye. PAMAM dendrimers with carboxylic or hydroxyl surface groups, have been reported in increasing residence time and enhancing bioavailability of pilocarpine in the eye. In the New Zealand albino rabbit model, the residence time of pilocarpine in the eye was increased by using dendrimers with carboxylic or hydroxyl surface groups. These surface-modified dendrimers were predicted to enhance pilocarpine bioavailability[22].

Conclusion

Ocular drug delivery systems provide local as well as systemic delivery of the drugs. In conclusion an ideal ophthalmic drug delivery system include, In situ gel forming, ocular insert, micro emulsion, niosomes, nanoparticals, nanonsuspension, liposomes, dendri-mers. And other conventional ophthalmic dosage form such as solution, suspension, emulsion, eye drop, ointment, spray, viscous solutions, gels etc. The novel advanced delivery systems offer more protective and effective means of the therapy for various diseases of eyes. Stability is the major improvements are required in each system.

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